Patent Expedient No. PA/a/2006/009833
Patents Division Direction
Division's Sub Direction for the Examination of Biothechnologic, Pharmo-chemical and Chemical Area
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(FJAR)

**Object : Response to the Requisites Official Note.**
**C. General Director of the Mexican Industrial Property Institute.**

I am referring to the patent application that in representation of

ACTELION PHARMACEUTICALS LTD.

is being processed in the expedient cited at the heading and in particular to your kind Official Note No. 34103 dated April 28th 2009, the same that was notified to me May 7th 2009, whereby it is asked to me to fulfil the requisites indicated therein within a delay of two and a half months from the day following the date of the notification of said Official Note, and that will come to an end July 8th 2009.

As an attempt to satisfy the demanded requisites, hereby I allow myself to answer to the referred Official Note with the presentation of the following:

- New pages 56-59 in the Claims Section in order to overcome the objections in the referred Official Note based furthermore in the arguments exposed hereinafter.
- New page 60 of the Abstract in order to provide continuity to the presented text.

With due respect, my principal permits himself to indicate that a new claim 1 is introduced and that it is related to the compound (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide or an acceptable pharmaceutical salt thereof.

The basis is found in preceding claim 8 and in example 2 in page 28/29 of the application as it was originally presented in English. The basis for the pharmaceutically acceptable salts can be found in the preceding claim 1 and in page 4, lines 4 to 8 of the application as it was originally presented in English.

The new claim 2 introduces the compound (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide in the form of a free base. The basis are the same as for new claim 1.

New claim 3 is introduced, wherein the acid component of the preceding pharmaceutically acceptable salt is additionally specified. The basis is the same as for new claim 1.

New claim 4 is introduced, and it is related to the compound (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide as an hydrochloride acid salt

The basis are found in example 2, in particular c) procedure III of the application as it was originally presented, which generates the compound as the hydrochloride salt.

New claim 5 is introduced, and it is related to the compound (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide as a crystalline hydrochloride salt that can be obtained by the procedure describe in c) procedure III of the application as it was originally presented.

Claim 9 has been suppressed.

Claims 6 and 7 have been renumbered (previously they were claims 10 and 12) and they have been wrote in order to reflect the introduction of new claims 1 to 5.

Claim 11 has been suppressed without prejudice.

New dependent claims 9 and 11 have been introduced.

All of the amendments are based in the application as it was originally presented.

Reject in respect to the document WO2001/068609 mentioned in the ISR:

The compound in the new current claim 1 is considered a novel selection in respect to document WO2001/068609. The document WO2001/068609 describes a broad compound category that comprises

among many others the compound of the present invention as it is hereby amended.

Furthermore, there is no teaching, suggestion or reason in the previous technique that can lead a skilled person in the technique to chose precisely the compound of current claim 1. Thereby current claim 1 has to be considered as non obvious, *prima facie* in respect to the previous technique.

The compound in current claim 1 (i.e. (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide contains, for example, the unique combination of the following structural characteristics:

- A moiety 3,4-dihydro-1H-isoquinolin-2-yl substituted with a methoxy in positions 6 and 7.
- A phenylethyl group corresponding to one of the substituents R5/R6 from WO2001/068609.
- A substituent in a para position of the phenyl ring of said phenylethyl group, that is a trifluoromethyl group.
- A non substituted phenyl ring that corresponds to one of the substituents R7/R8 from WO2001/2068609.
- A methyl group that corresponds to one of the substituents R9/R10 from WO2001/2068609.
- A specific absolute configuration.

  The document WO2001/068609 describes a broad category of compounds that comprises, among many others, the compound of the present invention. This category is exemplified with 341 compounds that present the following structural characteristics:

- Many compounds comprise a moiety 3,4-dihydro-1H-isoquinolin-2-yl substituted with methoxyl in positions 6 and 7.
- Three exemplified compounds described in document WO2001/068609 (i.e. Examples 110, 111 and 112) present a phenylethyl group that corresponds to one of the R5/R6 substituents if WO2001/068609. Said phenylethyl group in those compounds it is not substituted.
- None of the compounds presents a trifluoromethyl substituent in a phenyl ring of an aralkyl substituent that corresponds to one of the R5/R6 substituents in WO2001/068609.
- The two exemplified compounds described in WO2001/068609 (i.e., Examples 4, 5) present a phenyl ring that corresponds to one of the R7/R8 substituents in WO2001/068609.
- The three exemplified compounds described in WO2001/068609 (i.e. the examples 5, 75 and 105) present a small substituent (i.e. an alkyl) that corresponds to one of the R9/R10 substituents in WO2001/068609. There is no example of a compound presenting a methyl group in said position.

  The mentioned *Chimia* 2003, 270-275 publication (see page 3 of the application as it was originally presented in English) describes, for example, in Table 4 and in page 275, the compounds:

- 2-{6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-3,4-dihydro-1H-isoquinolin-2-yl}-N-butyl-2-phenylacetamide (compound 42, corresponding to Example 5 in WO2001/068609);
- 2-{6,7-dimethoxy-1-(naphtalen-2-yl-methyl)-3,4-dihydro-1H-isoquinolin-2-yl}-N-cyclopropyl-2-phenylacetamide (compound 44);

- 2-{6,7-dimethoxy-1-[2-(3,4-difluorophenyl)ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-butyl-2-phenylacetamide (compound 46); and
- 2-{6,7-dimethoxy-1-[2-(3,4-difluorophenyl)ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-cyclopropylmethyl-2-phenylacetamide (compound 47)

Nevertheless, the document WO2001/068609 of the previous technique and the mentioned *Chimia* publication, do not describe the unique structural characteristics of the compound in present claim 1, and the previous technique does not describe nor suggest any reason or motivation to select the specific compound of current claim 1 in its specific absolute configuration. As a matter of fact, the compound in the present invention is different from the compounds described in previous technique at least in three structural aspects.

Therefore, it would not be obvious *prima facie* to chose the substituents and the absolute configuration used in the compound of the present invention from the wide class of compounds described in the previous technique.

Therefore, current claim 1 is considered as non evident *prima facie* with respect to the reference WO2001/068609 of the previous technique and with respect to the mentioned *Chimia* 2003 reference.

Furthermore, the superiority of the compound of current claim 1 is demonstrated by the fact that currently the compound is under clinic development in phase III for primary insomnia (for more

details see, for example, the internet site of the company www.actelion.com).

In consequence, the inventive step is to be recognized for the present invention.

Considering that with the presentation of previous documentation, we have fulfilled the requests of the C. Examiner in the Official Note I am answering, I hereby beg you to instruct the continuation of the necessary procedures in order to confer the solicited patent to my principal, knowing that I proceed to the payment of taxes corresponding to the presentation of this documentation.

I hereby present my kindest consideration

Mexico, D.F. June 25th, 2009

pp. ACTELION PHARMACEUTICALS LTD.

Lic. Francisco Javier Uhthoff Orive

Representative

Attachments:

- New pages 56-59 from the Claims Section, in duplicate.
- New page 60 from the Abstract, in duplicate.
- General Declaration of Tax Payment.

**Notifications: Hamburgo 260, 06600, México, D.F.,**

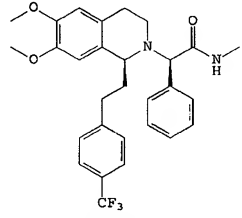
**Telephone 55 33 50 60**

RCP/ahp

**CLAIMS**

Having described the invention hereinbefore, we demand as property the contents of the following claims:

1. The compound (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide:



or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, characterized in that is (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide in the form of a free base.

3. The compound according to claim 1, characterized in that is (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide;

in the form of pharmaceutically acceptable addition salt of an acid.

wherein the acid component of the pharmaceutically acceptable salt is selected from the group consisting in hydrochloride acid, hydrobromide acid, hydroiodic acid, sulphuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, fumaric acid, benzoic acid, pamoic acid, stearic acid, methanesulfonic acid, p-toluenesulfonic acid, salicylic acid, succinic acid and trifluoroacetic acid.

4. The compound according to claim 1, characterized in that is the hydrochloride acid salt of (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide.

5. The compound according to claim 1, characterized in that is the crystalline hydrochloride acid salt of (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenylacetamide;

that can be obtained by

a) heating a solution of (1S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline (100 mg),

toluen-4-sulfonic acid (S)- methylcarbamoilphenylmethyl ester (100 mg) and diisopropylethylamine (0.063 ml) in butanone (5.0 ml) to reflux during 3 days and cooling the solution to room temperature;

b) adding ethyl acetate and washing the mixture with a $NaHCO_3$ saturated aqueous solution and brine;

c) drying the organic phase with $Na_2SO_4$ and elimination of solvents under vacuum;

d) adding THF (2.0 ml) and a solution of HCl in isopropanol (5-6 M, 0.10 ml) and separation of solvents under vacuum; and

e) recrystallization of the solid obtained from THF (2.0 ml).

6. A pharmaceutical composition characterized in that it has at least one compound according to any of claims 1 to 5 and a pharmaceutically acceptable carrier material.

7. The use of a compound according to any of claims 1 to 5 for the preparation of a medicament for the prevention or treatment of a disorder or disease selected from the group consisting in feeding disorders or sleeping disorders.

8. The use according to claim 7, wherein the feeding disorders comprise metabolic dysfunction,

control of non regulated appetite, compulsive obesity, emeto-bulimia or anorexia nervosa.

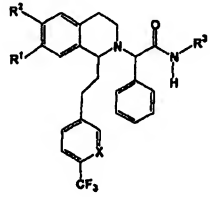
9. The use according to claim 7, wherein the disorder or disease is a sleeping disorder.

10. The use according to claim 9, wherein the sleeping disorders comprise insomnia, narcolepsy, and other excessive sleeping disorders, sleeping related distonies, restless leg syndrome, sleep apneas, time inconvenience syndrome, shift-work syndrome, delayed or advanced sleep phase syndrome.

11. Use according to claim 9, wherein the sleeping disorder is insomnia.

**ABSTRACT**

The invention refers to novel 1,2,3,4-tetrahydroisoquonolin derivatives of formula (I) wherein $R^1$, $R^2$, $R^3$ and X are as defined in the Claims section, and to their use as active ingredients in the preparation of the pharmaceutical compositions. The invention also refers to related aspects including processes for the preparation of the compounds, pharmaceutical compositions that contain one or more of this compounds and to treatment methods that comprise the administration of the compounds to a mammal.

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